PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
100632-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE 2003/000508	28.03.2003	28.03.2002
International Patent Classification (IPC) or national classification and IPC		
C07D 401/04, 403/04, 401/14, 403/14, 413/14, A61K 31/404, 31/4427, 31/495, A61P 25/28, 25/00, 3/10, 15/16		
Applicant		
AstraZeneca AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

   ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

   ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

   _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.10.2003	01.03-2004
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/000508

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/000508

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 18-22

because:

☒ the said international application, or the said claims Nos. 18-22 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 13 in part are so unclear that no meaningful opinion could be formed *(specify)*:

The expression "conditions associated with glycogen synthase kinase-3" in claim 13 may relate to a number of different disorders and conditions, which can not be clearly defined by this expression. Thus, the search has mainly been restricted to the diseases mentioned in claims 14-17.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 25-33,40 and 41 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. IV Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☐ not complied with for the following reasons:

The present application has been considered to contain four inventions which are not linked such that they form a single general inventive concept, as required by Rules 13.1, 13.2 and 13.3 PCT for the following reasons:

According to Rules 13.1 and 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features that define a contribution which each of the inventions makes over the prior art. In order to fulfil the requirements of unity of invention, it is necessary that the intermediate compounds are closely interconnected with the end products as well as with themselves. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate. However, the present application lacks a single general inventive concept based on the above principle. This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept.

I: Claims 1-24, 34-39 and 41 in part directed to compounds according to formulae Ia, Ib, XXVII and XXVIII, pharmaceutical formulations comprising these compounds, use, process and

.../...

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-24, 34-39 and 41 in part

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box No. IV

intermediates for the preparation thereof.

II: Claims 25-27 and 41 in part directed to compounds according to formula XXV and their use as intermediates.

III: Claims 28-30 and 41 in part directed to compounds according to formula B (XV, XVIII, XVIIIa, XXI, XXIII) and their use as intermediates.

IV: Claims 31-33, 40 and 41 in part directed to compounds according to formula C (III, V, IX, XII, XIII) and three compounds specified in claim 40 and their use as intermediates.

The ISA has carried out a partial search which relates to the invention I mentioned above.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/000508

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-24, 34-39 and 41 in part	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-24, 34-39 and 41 in part	NO
Industrial applicability (IA)	Claims	1-24, 34-39 and 41 in part	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The opinion given is based on what is searched. Confer part III and part IV in this report and PCT Rule 66.1(e).

The following relevant documents are cited:

D1) WO 0125200 A1 (KINETIX PHARMACEUTICALS INC.), 12 April 2001 (12.04.01), RN333730-27-1, 333728-93-1, page 89, no. 517, page 220, page 303, page 320, page 335, page 348, page 353, page 3, line 1 - page 4, line 2, the claims

D2) WO 0210158 A2 (F.HOFFMANN-LA ROCHE AG), 7 February 2002 (07.02.02)

D3) WO 0071129 A1 (BRISTOL-MYERS SQUIBB COMPANY), 30 November 2000 (30.11.00), page 9, line 28 - page 10, line 6; page 13, line 28 - page 14, line 12; page 81, line 25 - page 88, line 2, the claims

D4)WO 0132653 A1 (CEPHALON, INC.), 10 May 2001 (10.05.01), page 14, line 24 - page 30; page 69, no. 297, page 80, the claims.

D5) WO 9742187 A1 (ZENECA LIMITED), 13 November 1997 (13.11.97), page 2, line 17 - page 3, line 4; page 31, line 20 - line 29, the claims

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box No. V

D1 discloses compounds, structurally close to the presently claimed compounds, having kinase modulating activity and useful e.g. for the treatment of disease and conditions of the central nervous system (CNS). Thus, that is the same use as the presently claimed compounds. The presently claimed compounds differ by P being a 5- or 6-membered ring containing one or two heteroatoms instead of a triazine ring according to D1.

D2 disclose compounds, structurally close to the presently claimed compounds, having having glycogen synthase kinase 3 beta activity and useful e.g. for the treatment of Alzheimer's disease. Thus, that is the same use as the presently claimed compounds.

D3 to D5 disclose compounds, structurally close to the claimed compounds, having partly the same therapeutic effect.

The closest prior art to the present subject-matter is regarded as being represented by documents D1 and D2. In the light of the prior art and having regard to the present description and claims, the problem underlying the present application can be formulated as "provision of further modulators of glycogen synthase kinase-3 activity useful in the treatment of a wide range of glycogen synthase kinase-3 mediated conditions".

No inventive concept can be recognised in the mere provision of further analogues to existing pharmaceutical compounds unless the novel compounds are shown to possess an unexpected and advantageous effect over the prior art (i.e. D1 and D2, and confer as well D3 to D5).

None of the cited documents has explicitly disclosed the invention claimed in claims 1-24, 34-39 and 41 in part. Thus, claims 1-24, 34-39 and 41 in part are novel. However, given the facts above the subject matter of claims 1-24, 34-39 and 41 in part is considered obvious to a person skilled in the art. It has not been shown, for the whole scope of the claims, that the invention claimed in claims 1-24, 34-39 and 41 in part has any unexpected beneficial effects compared to those in the cited documents.

In the absence of an unexpected effect inventive step is considered to be lacking.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box No. V

Consequently, the invention claimed in claims 1-24, 34-39 and 41 in part is novel, is considered to fulfil the requirement of industrial applicability, but is not considered to fulfil the requirement of inventive step.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The expression "conditions associated with glycogen synthase kinase-3" in claim 13 may relate to a number of different disorders and conditions, which can not be clearly defined by this expression. See PCT Article 6.